

## **Improving Sedation in Intensive Care: New drugs or better methods?**

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## **Abstract:**

**Background:** Over-sedation has significant impact on intensive care resources and patient outcome. Recent protocols that constrain and/or interrupt sedation delivery have reduced resource utilisation but have not significantly addressed difficulties in agitation control. Thus, patient outcomes have not changed significantly. The primary objective of sedation delivery in critical care is to control patient agitation at a minimum sedation concentration. Thus, it is a balance between minimizing sedation delivery and managing acute, and sometimes quite significant, episodes of patient agitation. In particular, agitation episodes tend to be sudden, “spiky” or acute, while, for convenience, sedation delivery tends to be continuous. Hence, many current methods and therapeutics used to control patient agitation are not matched to what is demanded by patient behaviour. This review examines sedation management in critical illness and explores how new methods of sedation delivery and new therapeutics can offer advantages over accepted practice.

**Methods:** The current literature is reviewed and results summarized to compare and contrast differing approaches to sedation administration. In particular, emphasis is placed on randomized control trials (RCTs) in the past 5 years highlighting new and existing methods of employing well accepted, existing drug therapies. Over 30 such articles were found and their results summarized for analysis in terms of drug type, critical care unit type.

**Results and Outcomes:** There currently exists no common approach to sedation therapy delivery due to a lack of full understanding of the underlying dynamics (both pharmacological and physiological). In particular, despite a large range of therapeutics, the majority of studies (over 65%) focused on new drug types at the expense of the most commonly used therapeutics. Many studies were hard to compare due to different definitions or applications of patient agitation resulting in potentially very different outcomes for otherwise similar protocols. In addition, different target patient groups and very short term studies with no long-term outcomes also made further analysis difficult. As a result, sedation delivery is still very much a custom therapy, delivered individually to each patient, with great variability across patients and units.

**Conclusions:** The lack of an underlying framework or structure for sedation delivery that is based on a first principles approach to therapy should be a focal point for new research. Questions as to the underlying causes of patient agitation and the specific physiological and psychological goals of sedation delivery should be addressed to provide the foundation for consistent best practice methods. In particular, there is a desperate need for an objective, repeatable and entirely non-subjective approach to measuring or quantifying patient agitation before we can begin to develop a consensus on how best to treat or manage it.

## **1.0 Introduction:**

The direct costs of sedation were estimated to range from \$0.8-1.2 billion USD in 2001 [1]. However, the indirect costs through excess bed days due to over-sedation might be as high as a third of the total cost of care in some patients if the results of Kress and colleagues are to be extrapolated more generally [2]. It would thus be plausible to speculate suboptimal sedation management and/or delivery results in, at least, a 5% loss in bed space capacity to care for critically ill patients – in essence, over sedated patients take up beds.

In particular, intensive care is, in essence, 'expensive' care and its resources are expected to diminish. In contrast, the costs of intensive care, by almost every measure, continue to increase [3-5]. In addition, demographics and the rapid rate of growth of chronic diseases like diabetes will further compound the demand side of this equation [3]. Hence, lost capacity, resulting from any cause, is not just an intensive care problem, but instead a global health issue because resources for all aspects of healthcare ultimately compete for the same limited sources of funding no matter the specific structure of the health care system.

In the cluttered, confusing, highly dynamic and complex intensive care environment, it is not uncommon to find recently graduated nurses and resident doctors struggling to control a highly agitated patient. In particular, persistent patient agitation can well be a significant issue for any doctor, regardless of experience. The end result is typically significant over sedation, an easy solution that makes the problem disappear, but comes with an, admittedly difficult to measure, added cost in patient stay.

Until recently there were no specific, evidence based protocols to guide sedation therapy. The development of nursing-led sedation protocols has significantly reduced length of stay [6]. In addition, sedation interruption based regimes following on from Kress et al have been tested extensively, as well [7-12]. However, to date, truly protocol based sedation delivery has not been widely adopted in intensive care [13-15].

The importance of sedation management is has gained greater appreciation by all critical care practitioners over this decade since the publications of Brook et al and Kress et al, as evidenced by the growth in publications. However, the translation of this research into clinical practice has been woeful. The real question should focus perhaps on, why?

Perhaps, as a field, we are looking in the wrong places for answers to this vexatious problem. In a PubMed search of randomised controlled trials (RCTs) of sedation management in intensive care (key words: *sedation, intensive care*) from Jan 2004 to Oct 2008, of the 30 randomised controlled (clinical) trials (RCTs) almost 74% solely compared the impact of one or more drugs on an aspect or consequence of sedation. The remainder focused on the context and how sedation drugs were used. These studies included the impact of sedation scores, algorithms (including sedation interruption) and weaning from mechanical ventilation.

What is glaringly absent is any research focus, or even interest, is the development of systems or methods to both quantify sedation and appropriately deliver sedation by methods that are simple, consistent, and reliably control agitation. It seems that in the quest for finding new and better drugs we have been putting all our eggs in the one "new therapeutic" basket, with very disappointing progress in this important aspect of healthcare.

The problem is the consistent management of critically ill patients' sedation and analgesia is in fact extraordinarily difficult; one reason why sedation management remains one of the most arbitrarily applied therapies in all of medicine. Why should this be so?

## **2.0 Wrong goals, wrong treatment, and wrong diagnosis**

Sedation and analgesia in critical care are most often given to manage agitation and pain. Unlike anaesthesia, the goal of intensive care sedation is diminish the levels of patient exhibited agitation and pain. Thus, it is not used to primarily produce hypnosis and analgesia,

which is the primary goal of anaesthesia and a key differentiator of the two otherwise similar appearing therapies.

As a result, the goals and methods used to assess and control intensive care sedation should necessarily be quite different than those used to assess anaesthesia. While it is true that high levels of anxiety and pain ultimately create an agitated state, it is also true that high levels of opioids and hypnotics will diminish agitation from whatever cause. However, what is left unsaid is that there are potentially many other causes of agitation in the intensive care unit patient.

In particular, cardiovascular dysfunction (e.g. acute heart failure), ventilator dyssynchrony, delirium, and other physical and environmental factors (e.g. lights, noise) can create an agitated state. More importantly, it is critical that these factors should always be managed by specifically treating the underlying causes, rather than adding sedation. The problem is the 'wrong' diagnosis of these issues, some of which are difficult to detect or specifically identify (e.g. delirium vs "true" agitation) and a resulting 'wrong' treatment results in what appears, at least in the short term, to be the 'right' result.

However, as noted, the long term consequences are over sedation. It can also be very difficult, if not impossible, to extricate the underlying causes of agitation in many critically ill patients. The real missing link however is the unfortunate lack of research into development of protocols that can more optimally manage these diverse patient-specific variables to specifically guide staff through this difficult process.

### **3.0 Driving blind**

It is useful to contrast glucose and agitation control. Both use therapeutics with similar kinetics and both have action sites that are not directly measurable. What differentiates them is the ability to measure glucose versus our inability to objectively quantify agitation.

More specifically, blood glucose can be measured simply, precisely reliably, and consistently. In addition, its primary therapeutic, insulin, has readily known kinetics, and its dynamic interaction to remove glucose is also well understood. Short-term glucose control is thus effectively well managed through therapeutics and modulation of nutrition. The responses are usually predictable, and many technologies are available to assist drug delivery.

Contrast this with agitation control. The metrics used to quantify agitation have very poor resolution, are subjective and unreliable [1, 15-17]. This issue is further complicated by multiple choices of therapeutics and other non-therapeutic interventions that may be appropriate (e.g. ventilator adjustment vs more sedation or analgesia for ventilator dyssynchrony). The patient's responses may also be highly variable being influenced by unknown pharmacokinetics and dynamics.

The problems poor measurement and resolution are exemplified by the Richmond agitation scale [17] where patients are graded on a 10 point nominal scale ranging from severe agitation to deep sedation. However, the desirable range or 'sweet spot' has a nominal scale of only three points, light sedation through to awake and calm (-2, -1, 0). There is also no guidance regarding what would constitute the appropriate resulting amount of sedation or analgesia required.

A recent RCT comparing daily interruption of sedation and nursing-implemented sedation algorithm from de Wit and colleagues [8], used a modified protocol from Brook et al [6]. However, the specific therapeutic guidelines were comparatively coarse. If over-sedated there are provisions for stopping or reducing the infusion rate by 25% or 50%, and if agitated a moderately large bolus of midazolam, lorazepam, or fentanyl may be given. However, no quantified definition that would be objectively consistent was available to define these states.

More concisely, the primary problem is that the ‘human sensor’ lacks resolution and is not objective. In addition, these measured control outputs are highly and non-linearly discretised, which ultimately leads to poor control. Given the highly dynamic state of the acute care patient, this situation is akin to driving with one’s parking lights on a moonless night, ... on a winding dirt road, ... in a car with unreliable steering and brakes. Even a great deal of attention and experience can result in one going off the road, unless one drives so slowly that “the patient” takes far too long to arrive at their destination.

In simpler terms, given the tools at hand, it is easy to over sedate a patient and accept the long time to wean and increased length of stay, where managing sedation to a minimum requires attention, effort and knowledge that are simply not currently available. To “turn the lights on and smooth out the road” would require not better drugs, but better sensors. Thus, it might be said that the state of the art of sedation management is, by and large, driving blind.

#### **4.0 What is needed?**

Three broad areas of research are required to improve current state-of-the-art management of agitation in critical illness:

1. A quantified, objective agitation scale based on measurable physiological metrics
2. Validated models of the pharmacodynamics and pharmacokinetics associated with patient agitation and sedation to improve knowledge and understanding.
3. Effective and well understood drug administration (and non-therapeutic) protocols resulting from using the first of these points with the second to develop new, protocolised approaches to this problem

How can one make better sense of agitation, how can it be measured? Agitation might be described as a heightened level of physical and autonomic activity in response to any stimulus or stimuli, which either threatens or disturbs the equilibrium of that individual. The definition is clearly broad as it includes, for example, the responses to perceived threats or actual physical harm. However, in spite of the many causes of agitation, its manifestations are fewer and can be quantified.

An objective measure of the physical changes (movement or grimace) together with autonomic changes (blood pressure, heart rate, and their changes or variability) may be taken together to give a global metric of agitation [18-20]. A proof-of-concept agitation sensor has been validated in a cohort of critically ill patients by comparing an ‘agitation index’ with the sedation-agitation scale of Riker [21]. Further refinements include the quantification of grimacing and biting of the ET tube [18].

This agitation sensor, or any similar development, offers the potential to assist agitation measurements by providing consistent and objective metrics of the patient-specific state of agitation. In the first instance, this device might assist nursing staff in drug selection dose and

timing. This concept might be intensive care's answer to the bi-spectral index (BIS) which informs the anaesthetists of the likelihood of awareness during anaesthesia [22]. Given the different goals of the anesthetist and critical care nurse in managing their respective problems, it is not plausible to use the same sensor [14, 23-26].

To better understand agitation dynamics a pharmacodynamic model is required. In its simplest form, the model is based on the following premise: the rate of change in agitation depends upon the relative magnitude of the stimulus compared to the cumulative effect of sedation. In other words it balances the impact of sedation with the level of agitation. This model, together with a proportional derivative controller has been used to create a 'virtual nurse' that captures the dynamics of sedation infusion and patient response to any protocol or clinical behaviour [27-30]. Sedation administration data from intensive care patients receiving a fixed mixture of morphine and midazolam as dosed using a semi-automated open loop sedation delivery system, the Infuserite [14], resulted in two important behaviours being observed.

First, clinical staff delivers sedation according to the rate of change of agitation. Second, the rate of change and level of agitation can be minimised by increasing the bolus size (controller gain). This result has important implications. Sedation scores cannot record rates of change in agitation, yet this remains the key metric by which drug infusions currently are titrated. The finding that increasing bolus size reduces the magnitude and duration of agitation as well as the total amount of drug required lends support to the notion that sedation infusions contribute to over-sedation. Ultimately, a bolus driven approach, where the bolus is tuned to the patient's response, would be a significant improvement on current practice.

## 5.0 Summary

There remains a huge gap in clinicians' knowledge of sedation-agitation dynamics. The few published protocols of sedation management use crude ad-hoc heuristics, which do not capture the fundamental dynamics of patient agitation. None of these protocols have been developed from modelled simulations of sedation-agitation dynamics. This type of modeling has taken insulin delivery in the management of blood glucose to a highly refined art. In the case of sedation management, these modeling methods, with an appropriate consistent and objective agitation sensor can do the same to provide highly optimised and patient-specific sedation delivery.

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